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Therapy in myotonic disorders and in muscle channelopathies

Abstract Myotonia and muscle weakness are cardinal features of myotonic disorders including the myotonic dystrophies and the non-dystrophic myotonias. Despite the recent progress in molecular genetics of these myotonic disorders, the precise mechanisms responsible for myotonia and for permanent or episodic muscle weakness are still unclear. Treatment has been mostly symptomatic, independent of the disease process involved. Moreover, there have been few randomized controlled trials of treatment for myotonic disorders and consequently no standardized treatment regimens are available. We present a review of selected treatment trials in the myotonic disorders and in muscle channelopathies, and discuss, on the basis of our experience in the myotonic disorders, the limits and advantages of treatment trials in this field. Future genotype-phenotype correlations using the patch-clamp technique are also illustrated.

Key words Myotonic disorders • Muscle channelopathies • Therapy

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Introduction

Muscle weakness and myotonia are cardinal features of myotonic disorders including the myotonic dystrophies (myotonic dystrophy type 1, myotonic dystrophy type 2, proximal myotonic myopathy, and proximal myotonic dystrophy) [1-3] and the non-dystrophic myotonias (sodium, calcium and chloride channelopathies and Andersen's syndrome) [4-11]. In this review, we focus on the non-dystrophic myotonias in which genetic and physiological studies have provided a reasonably complete view of the pathophysiology of these ion channel disorders (Table 1) [4, 7, 8].

Table 1 Classification of the non-dystrophic myotonias

Sodium channel diseases (SCNA4)
Hyperkalemic periodic paralysis
Paramyotonia congenita
Potassium-aggravated myotonia
Myotonia fluctuans
Myotonia permanens
Acetazolamide-responsive myotonia
Chloride channelopathies (CLCn1)
Thomsen's (autosomal dominant)
Becker's (autosomal recessive)
Calcium channelopathies
Probable channelopathies
Andersen's syndrome
Schwartz-Jampell syndrome

Table 2 Selected trials of treatment in myotonic dystrophy type 1 (DM1)

Reference	Patients, n	Type of trial	Treatment regimen	Evaluation criteria	Comments
Orndahl et al. [70]	1	Open	Selenium (3 mg qid), vitamin E (300 mg) for 2 years	Functional tests	Improvement on functional tests
Orndahl et al. [69]	5	Open	Selenium (4 mg qid), vitamin E (600 mg)	Functional tests and grip dynamometry	General improvement
Orndahl et al. [68]	27	Double-blind placebo-controlled	Selenium (1.6 mg qid), vitamin E (800 mg) for 2 years	Muscle strength, max walking speed, daily disability scales	No conclusive beneficial effect
Guilleminault et al. [18]	6	Open	Baclofen (60 mg qid)	36-h sleep polygraphy, dynamometry and electromyography	No beneficial effect
Kwiecinski [71]	1	Open	Acetazolamide (250 mg qid)	Subjective evaluation of myotonia severity	Improvement of myotonia
Finlay [72]	10	Cross-over	Procainamide (500 mg q6h) Disopyramide (200 mg q8h)	Manual muscle strength before and after treatment and clinical severity of myotonia	No difference between the two drugs. Decrease in myotonia. No difference in muscle strength
Sechi et al. [73]	6	Double-blind	Phenytoin (200-300 mg qid) Carbamazepine (600-800 mg qid) Each preceded by placebo	Myotonia assessed on a 4-point arbitrary scale (1, absent; 4, severe) for chewing, opening fist and walking and by relaxation time after 2-s MVC	Improvement of myotonia with both drugs
Mamoli et al. [20]	3	Open	Sodium dantrolene (120 mg qid)	Strength and myotonia assessed by relaxation time	Improvement of myotonia but decreased muscle strength
Mielke et al. [74]	10	Open	Tocainide (800-1200 mg qid)	Subjective and objective tests for myotonia	Improvement
Grant et al. [75]	10	Single-blind cross-over	Nifedipine (10 or 20 mg tid for 2 weeks)	Grip strength and fatigability before and after treatment	No conclusive beneficial effect
Fitting et al. [15]	1	Open	Procainamide	Myotonia of respiratory muscles measured by transdiaphragmatic pressure	Beneficial effect on dyspnea and tachypnea but treatment discontinued because of lupus-like syndrome
Griggs et al. [17]	40	Double-blind	Testosterone enanthate (3 mg/kg wk) over a 12-month period	MMT, QMT, pulmonary function and quantitative functional assessment	No improvement of strength
Gasgon et al. [16]	12	Double-blind cross-over	Imipramine (150 mg for 6 weeks)	–	Improvement
Milner-Brown, Miller [21]	12	Open	Amitriptyline (50 mg qid for 4-6 months)	Muscle strength assessed by 5-s MVC, myotonia assessed by measuring relaxation times at 50% and 75% decline of MVC	Myotonia improved, strength unchanged
Backman, Henriksson [12]	15	Open	Selenium, vitamin E for 2 years	Myotonia assessed by relaxation time	Improvement

Table 2 Contin.

Reference	Patients, n	Type of trial	Treatment regimen	Evaluation criteria	Comments
Sugino et al. [22]	11	Open	DHEA-S (200 mg qid for 8 weeks)	Functional tests, muscle strength, myotonia	Improvement of ADL, muscle strength and myotonia. Improvement of conduction blocks and premature beats
Kashiwagi et al. [19]	1	Open	Troglitazone (400 mg qid)	Insulin resistance by glucose infusion rate during a euglycemic hyperinsulinemic clamp and myotonia evaluated by functional tests and grip myotonia by muscle strength in kg	Improvement of insulin resistance, grip strength and myotonia
Tsuji K et al. [25]		In vitro	DHEA-S		Possible improvement of muscle strength and myotonia following replacement therapy in myotonic dystrophy given the role of DHEA-S on skeletal muscle in normal conditions and its reduction in serum from patients with myotonic dystrophy

MVC, maximum voluntary contraction; *MMT*, manual muscle testing; *QMT*, quantitative muscle testing; *DHEA-S*, dehydroepiandrosterone sulfate; *ADL*, activities of daily living

Myotonic dystrophies

Recent molecular studies have classified the myotonic dystrophies into 3 groups according to the chromosome involved: myotonic dystrophy type 1 (DM1) is linked to chromosome 19q13.3; myotonic dystrophy type 2 (DM2), proximal myotonic myopathy (PROMM) and proximal myotonic dystrophy (PDM) are linked to chromosome 3q21.3; and the remaining families with DM-like phenotypes unlinked to chromosome 3q21.3 still await classification and should be referred to as DMn, suggesting a third (or more) disease loci [3]. Given the clinical similarities to myotonic dystrophy, first described by Steinert in 1909 [11a], and the same type of multisystem involvement, it is likely that the same molecular mechanisms are involved in these disorders. However, despite the genetic progress in this field, the gene lesion responsible for the clinical manifestation is still unknown and the pathophysiology of this group of muscle diseases is still unclear. Nonetheless, treatment for muscle weakness and myotonia has been proposed by several authors [12-26]. A summary of selected treatment trials in myotonic dystrophy type 1 is given in Table 2.

Non-dystrophic myotonias

The non-dystrophic myotonias include disorders of voltage-gated skeletal muscle ion channels grouped under the term "periodic paralysis". These are hereditary disorders that share the common phenotype of episodic muscle weakness or paralysis in the absence of abnormalities of the motor nerve, neuromuscular junction, or contractile proteins [27]. In periodic paralysis, weakness is often accompanied by characteristic changes in the serum potassium levels which have formed the basis for the traditional classification into hyperkalemic and hypokalemic periodic paralyses. These disorders are associated with depolarization of the muscle sarcolemma during episodes of weakness. In each variant, depolarization is produced by an increase in sodium conductance [28-34]. For hyperkalemic periodic paralysis and paramyotonia congenita, this pathological increase is triggered in vitro by increasing extracellular K^+ or by cooling the muscle fiber, respectively, and the abnormal conductance can be blocked by the specific muscle sodium channel blocker tetrodotoxin (TTX), thus implicating sodium channels in the pathophysiology of both diseases.

Sodium channelopathies

Hyperkalemic periodic paralysis

The gene locus for sodium channelopathies (SCN4A) has been defined and the classification of these disorders has recently been clarified [9, 35-38]. On the basis of plasma

potassium levels during an attack of paralysis and on the basis of the effect of potassium administration on the strength of patients with a sodium channel mutation, this channelopathy is also known as potassium-sensitive periodic paralysis. Many disorders characterized by potassium sensitivity localize to chromosome 17q23.1 and are related to abnormalities of the alpha-subunit of the sodium channel [9, 28, 32, 38-45]. From the clinical and laboratory viewpoints, sodium channelopathies are heterogeneous disorders: the potassium level during an attack may be normal, elevated and in some occasions even low during an attack of paralysis and may vary between attacks and between individuals within the same family. Inheritance is normally autosomal dominant. Onset of attacks of weakness is usually in the first decade of life. The attacks are usually brief and mild in most cases, usually lasting several hours. Triggers for the attacks are rest following exercise and fasting. During rest, after a period of exercise, there is a small increase of extracellular potassium. This causes a slight membrane depolarization. There is an opening of sodium channels but also a shift of sodium channels to the non-inactivating mode so that there is a persistent inward sodium current which causes a sustained depolarization of the membrane. This leads to either an efflux of potassium and a further increase of extracellular potassium or to the inactivation of normal sodium channels with loss of electrical excitability and thus the paralytic attack. Weakness affects muscles in a shoulder and pelvic distribution, and is usually symmetrical and severe enough to determine transitory paralysis. Muscles are typically hyporeactive and tendon reflexes cannot be elicited during an attack. In the intercritical period patients usually have muscles of normal bulk and strength. Only in some cases has permanent weakness been described.

Myotonia, instead, is usually prominent on both clinical and electromyographic evaluation at any time in patients with potassium-sensitive periodic paralysis. It is usually present in the hands and eyelids, and improves with exercise (warm-up phenomenon). In sodium channel myotonia, the degree of myotonia among different families is particularly variable. For this reason, fluctuation of myotonia, particularly with potassium ingestion, was considered characteristic of sodium channelopathies. However, there has been a report of a large family with fluctuating myotonia which resembled the fluctuations of sodium channelopathies, in which the genetic defect was clearly localized to the chloride channel [46].

Paramyotonia congenita

This autosomal dominant disorder, first described by Von Eulenberg a century ago (in 1886) [46a], is characterized by paradoxical myotonia. Exercise worsens the myotonia rather than improving it, as is typical of the warm-up phenomenon of myotonia. Triggers are also different compared to hyperkalemic periodic paralysis: myotonia can be exacerbated by cold, and attacks of weakness, if present, may also be precipitated by cold exposure. This disorder is allelic to the hyperkalemic periodic paralysis gene locus on chromosome 17q. It involves distinct mutations of the alpha-subunit of the sodium channel [38, 43, 45]. As more mutations are identified, the clinical differences between these disorders are less clear [47]. Families with overlapping symptoms have been described. Rather than being distinct pathophysiological entities, these disorders form a continuum in which the specific features of a given family depend critically on the nature and location of their unique mutation.

Chloride channelopathies

The chloride channel found in skeletal muscle is the chloride channel type 1, encoded on chromosome 7q35 [6]. More than 20 missense mutations, four nonsense mutations, three deletions, one insertion and two splice mutations in the gene have been identified [31]. Mutations in the gene encoding the skeletal muscle chloride channel CLCN1 are involved in two forms of myotonia in man: the autosomal dominant disease myotonia congenita first described by Thomsen in 1876 [4a] and the recessive myotonia congenita described by Becker in 1957 [4b]. Both diseases are characterized by muscle stiffness (myotonia) which results from the continued firing of action potentials in the muscles after the cessation of voluntary effort or stimulation. This results, like for other myotonic disorders, in a characteristic repetitive discharge in the electromyogram. The autosomal dominant form usually is present at birth whereas the recessive form develops during the first or second decade, beginning in the legs and progressing to the arms, neck and facial muscles. The recessive form of myotonia congenita is more common in men than in women, suggesting a reduced penetrance in women or that the disease, for some hormonal influence, has a milder phenotype. Symptoms are usually more severe in the recessive form compared to the dominant form. In both forms the myotonia is accentuated by rest and gradually relieved by exercise. A distinctive feature of chloride channelopathy is that weakness and myotonia usually appear after a period of rest, triggered by exercise. In the sodium channelopathy instead, the opposite happens: it is rest following exercise which triggers the attack. The patient with a chloride channelopathy, in fact, although able to walk normally, may suddenly fall if he or she tries to walk or run following a period of rest [46]. A gradual warm-up alleviates many symptoms. Patients usually have muscle hypertrophy as a consequence of the continuous muscle activity.

Electrophysiological studies using the patch clamp technique have been applied to study the expression of CLCN1 channels bearing myotonia-causing mutations [48]. These have demonstrated either a marked reduction, or the complete loss of the whole-cell chloride current. Analysis of four missense mutations producing dominant myotonia showed that they cause a marked shift in the voltage-dependence of steady-state activation to more positive potentials. This shift in voltage dependency is sufficient to prevent the channel from contributing to repolarization of the action potential and so pre-

disposes to myotonia. Although these dominant mutations cause a common phenotype, they occur at diverse locations throughout the protein. The fact that the structure of the chloride channel is far from resolved makes it difficult to postulate how they affect channel gating. For the recessive form of myotonia, it is expected that individuals heterozygous for the mutation possess half the number of normal chloride channels, consistent with the idea that a reduction of more than 50% of the chloride channel is required to cause the myotonic phenotype. Still more puzzling is how mutations in the same gene give rise to both dominant and recessive forms of myotonia. The explanation probably depends on the extent to which the wild-type subunits are inactivated [4, 8]. Another characteristic feature of myotonia congenita is that, in agreement with the clinical picture described above, repetitive muscle activity is worse after a period of rest and is alleviated by exercise. It is possible that this amelioration results from the enhanced activity of the muscle Na/K ATPase induced by exercise, which facilitates the clearance of K^+ ions from the T tubules.

Calcium channelopathies

Voltage-dependent calcium channels have been identified on the basis of their pharmacological properties [49]. One class of calcium channel proteins, the L-type channel, has been isolated using its affinity for dihydropyridines. Biochemically, these channels differ from sodium channels although the high degree of sequence conservation suggests that they are derived from the same primordial structure. The basic ion channel of this muscle protein, as well as its voltage-gated properties, are contained, like the sodium channel, within the alpha1 subunit. The other subunits play a role in interaction with cytoskeletal elements or with modulation of channel activity [28, 33, 40, 50-54]. Mutations in the voltage-gated skeletal calcium channel cause hypokalemic periodic paralysis [10]. This is a dominantly inherited disorder caused by mutations in the voltage-sensor dihydropyridine receptor [55]. Sporadic cases may occur. Most mutations occur in the fourth putative membrane-spanning segment of the receptor's fourth domain. The portion of the receptor containing mutations functions as a voltage sensor for the calcium channel. Muscle fibers become electrically inexcitable during attacks of weakness. The membrane potential is decreased during and between attacks with lowered potassium concentrations. The plasma potassium level falls during the paralytic attack usually below 3 mEq/l and levels below 2 mEq/l may occur [56]. Weakness may persist for hours after the return to normal potassium levels and plasma potassium need not fall below normal range during the attack of paralysis, suggesting that the fall in potassium level is the result of the attack of weakness rather than its cause. Triggers for paralysis are fasting, exercise and excessive liquorice intake. Onset of attacks is typically in childhood or young adulthood. Attacks usually occur in the morning and affect muscles in a shoulder and pelvic type of distribution, usually in a symmetric distribution. However, single limbs may be affected in a transitory manner. Tendon reflexes are unresponsive during an attack. Myotonia and muscle pain are not features of this disorder. Intercritically, more frequently than the sodium channelopathies, patients may have permament weakness with functional limitations in everyday activities. This girdle-type distribution of fixed muscle weakness is in agreement with findings of a vacuolar myopathy on muscle biopsy of patients with hypokalemic periodic paralysis. Progression is slow but significant.

Therapy for non-dystrophic myotonias

Table 3 illustrates selected trials of treatment in the non-dystrophic myotonias.

Sodium channelopathies

Local anesthetics and class 1b antiarrhythmic agents such as lidocaine, mexiletine and other lidocaine-derivatives have been tried to prevent muscle stiffness and cold-induced weakness of paramyotonia congenita [57, 58]. In contrast to the relief of stiffness and the prevention of cold-induced weakness, the spontaneous and potassium-induced attacks of weakness typical for hyperkalemic periodic paralysis and also occurring in many patients with paramyotonia congenita are not influenced by mexiletine at the doses of 200 mg tid [59]. Diuretics such as hydrochlorothiazide and acetazolamide (250 mg bid) can decrease frequency and severity of paralytic attacks by lowering serum potassium and perhaps by shifting the pH to lower values [7, 8, 29, 59, 60].

Chloride channelopathies

Many myotonia congenita patients can manage their disease without medication. When stiffness interferes with everyday activity and is associated with pain, treatment is recommended. Stiffness responds well to drugs that reduce the increased excitability of the cell membrane by interfering with the sodium channels, i.e. local anesthetics, antifibrillar and antiarrhythmic agents, and related drugs. These drugs suppress myotonic runs by decreasing the number of available sodium channels and have no known effects on chloride channels. Mexiletine is the drug of choice for these patients (200 mg tid) [61, 62].

Calcium channelopathies

In general, patients with hypokalemic periodic paralysis respond to acetazolamide (125 mg bid) [63]. The drug is generally well tolerated and reduces the frequency and

Table 3 Selected trials of treatment in the non-dystrophic myotonias

Reference	Patients, n	Type of trial	Treatment regimen	Evaluation criteria	Comments
Wang, Clausen [76]	15 HyperKPP	Open	Salbutamol inhalation	–	Alleviates hyperkalemia and paralysis precipitated by exercise and oral KCl
Johnsen [77]	5 HypoKPP	Open	Diazoxide (72 h exposure)	Degree of paralysis and level of hypokalemia before and after pre-treatment with diazoxide during induction tests for HypoKPP	Initial improvement with pre-treatment followed by adaptation
Torres et al. [65]	3 HypoKPP	Open	Acetazolamide	Frequency and severity of attacks of weakness	Increase in frequency and severity of attacks; improvement with triamterene
Dalakas, Engel [78]	3 HypoKPP	Single-blind placebo-controlled	Dichlorophenamide	Assessment of fixed weakness by QMT and frequency of attacks of weakness	Improvement of muscle strength and reduction of attack frequency
Links et al. [79]	8 HypoKPP	Double-blind cross-over	Acetazolamide	Muscle strength by handheld dynamometer; functional tests; surface EMG	Improvement in strength and in functional tests. No change in surface EMG
Ligtenberg et al. [80]	4 HypoKPP	Placebo-controlled double blind	Pinacidil (25 mg qid)	Muscle strength by handheld dynamometer in addition to assessment of insulin release during a hyperglycemic glucose clamp	Improvement of muscle strength in 2 of 4 patients with partial paralytic attacks
Hanna et al. [81]	1 HyperKPP	Open	Salbutamol inhalation	Clinical and electrophysiological monitoring	Improvement
Tawil et al. [66]	42 HypoKPP 31 K-sensitive PP	Two multicenter, randomized, double-blind, placebo-controlled crossover	Dichlorophenamide for 8 weeks; 9-week wash-out	Attack severity and frequency in HypoKPP; number of attacks per week in K-sensitive PP	Dichlorophenamide is effective in prevention of episodic weakness in both study groups

HyperKPP, hyperkalemic periodic paralysis; *HypoKKP*, hypokalemic periodic paralysis; *QMT*, quantitative muscle testing

severity of the attacks of weakness. These may become abortive, affecting only one limb and for a short period of time that does not limit the patient in everyday activities. Careful control of renal function and visual acuity is necessary. Treatment should be associated with a carbohydrate-poor, potassium-rich diet. We generally recommend 1600 kcal diets with a total of 64 g protein (16% of total kcal), 53 g lipids (30% of total kcal) 236 g carbohydrates (55% of total kcal intake).

Although the efficacy of the carbonic anhydrase inhibitors is well accepted as the first treatment of choice in primary periodic paralysis, some patients do not tolerate the drug [64], worsen [65] or become unresponsive. Recent trials involving another potent anhydrase inhibitor, dichlorophenamide, have suggested that it is effective in the prevention of episodic weakness in hypokalemic periodic paralysis and in potassium-sensitive periodic paralysis [66]. This drug has been previously recommended in the treatment of permanent muscle weakness in hypokalemic periodic paralysis which is a major concern for these patients.

Conclusions

Despite the major advances in molecular genetics in the myotonic disorders, little is known about the relationship between gene lesion and clinical manifestations of the myotonic dystrophies. Little is known about the structure and function of voltage-gated ion channels responsible for the known muscle channelopathies despite knowledge of the mutation involved. This is the reason why treatment strategies have been mainly symptomatic.

Identification of the channel involved does not substantially modify treatment strategies against either myotonia or muscle weakness. Considering myotonia, one should also bear in mind that although similar, each channelopathy has distinctive clinical features. Triggers for myotonia are different in the chloride channelopathies compared to the sodium channelopathies. Clinically, the myotonic phenomenon is expressed differently in these two ion channel disorders: it is severe and diffuse in the chloride channelopathies and inconstantly present and less pronounced in the sodium channelopathies. Yet antimyotonic treatment has often been the same for both disorders, based on empirical and anedoctical data. The same applies to treatment strategies against the attacks of weakness. Weakness in the sodium, chloride or calcium channelopathy has different characteristics. Clinically, on the basis of triggering factors, age at onset of attacks, frequency of the attacks and presence or absence of permanent weakness, it is possible to direct the diagnostic approach towards one channel or another. However, this does not substantially modify the treatment approach. In particular, the mechanisms involved in the development of permanent muscle weakness are still unclear so that only a few treatment strategies have aimed against its development.

Future treatment strategies should bear in mind the function of the protein and of the channel involved in the disease. Single-channel patch-clamp recordings of chloride channel currents from muscle fibers of known myotonia congenita mutations may, for example, demonstrate the specific effects of antimyotonic drugs like mexiletine which subjectively improves myotonia in these patients. We are currently studying chloride channel currents from patients with known chloride channel mutations to better characterize the mutated currents and study the effects of specific antimyotonic drugs on channel kinetics.

This approach may improve knowledge of channel function and therefore direct treatment strategies according to the mechanisms involved in the disease process [67]. Understanding the pathophysiology of this channelopathy may contribute to the understanding of other membrane-related disorders. DNA-based diagnosis will become a realistic proposition for most neurological channelopathies. Furthermore, it seems likely that new therapies will be designed based on genotype and mode of ion channel dysfunction.

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